Reviewer's report

Title: CHEK2 1100delC is prevalent in Swedish early onset familial breast cancer, a case control study

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Reviewer: Mieke Schutte

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General
The paper by Margolin et al. reports on the prevalence of the CHEK2 1100delC mutation in Swedish breast cancer cases. They identified the mutation in 0.7% of controls, in 0.3% of sporadic patients and in 2.2% of familial patients. The latter prevalence was significantly higher than in controls (p=0.03), indicating a breast cancer risk for the variant in the Swedish population. The approach and methods in the paper are sound. However, I have several comments on the manuscript:

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. At the end of the abstract (and at the end of the discussion), the authors state that the absence of an association of CHEK2 1100delC with sporadic cases and an influence of the mutation on age indicates a modifier role for the mutation. This conclusion is incorrect. A modifier role would be suggested by incomplete cosegregation, particularly in high-risk breast cancer families. Their data marginally support a modifier role, as they have DNA available from only a limited number of additional breast cancer cases from CHEK2 100delC positive families.
2. Results: Can the authors describe all ten CHEK2 1100delC positive families, in terms of numbers of breast cancer cases and of other tumour types?
3. The discussion is long and very unfocussed. In the first para, it is unclear what the point is that the authors want to make. In my view, the authors can conclude that CHEK2 1100delC associates with a breast cancer risk in their familial cases. Their sporadic cohort has insufficient statistical power to exclude a breast cancer risk and they therefore should refrain from drawing conclusions from this cohort.
4. The second para of the discussion is again too long and unfocussed. One wonders whether the authors are not over interpreting their age data. If the authors choose to discuss this item, they should address the selection criteria for the various cohorts in the literature. For example, familial cases will have earlier ages at diagnosis than sporadic cases irrespective of the CHEK2 1100delC mutation. Importantly, what are their ideas on their own results that the CHEK2 1100delC mutation frequency is 1.9% in the familial risk cohort and 2.9% in the familial cases from the population-based cohort whereas the age at diagnosis in the latter cohort is older than the familial cohort? Again, I do not believe that the age data are relevant, but if they choose to discuss it then they should take these points in account.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Materials
1. First para: from how many families are the 311 familial breast cancer cases derived? In other words, were the familial cases independent?
2. First para: How many of the 311 were tested for BRCA1/2?
3. Second para: can the population of southern Stockholm area be considered geographically and ethnically matched with the Karolinska hospital population where the familial cases and controls were recruited?
4. Third para, first sentence: are these familial cases from the population-based cohort or also from the familial risk cohort?
Methods
5. The mutation is known as CHEK2 1100delC and not del1100C.
Results
6. The actual numbers of familial, sporadic, high and low risk cases are all mentioned in Table 1A. They should also be mentioned somewhere in the text, either in the Results section or under Materials. Now, only some numbers are mentioned in the text.

Discretionary Revisions (which the author can choose to ignore)
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'